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TSCA section

8ECP

Submitting Organization

AMERICAN CYANAMID CO

Contractor

MB RESEARCH LABORATORIES

Document Title

INITIAL SUBMISSION: CT-470-91: PRIMARY DERMAL/OCULAR IRRITATION STUDY IN ALBINO RABBITS WITH COVER LETTER DATED 052992

Chemical Category

CT-470-91

4646

8(e)

CAP

(COMPLIANCE AUDIT PROGRAM)

TSCA CONFIDENTIAL BUSINESS INFORMATION

ORIGINAL - DCO (Jeff/Eric)

COPY # 1 - CBIC

COPY # 2 - Scott Sherlock

COMPANY SANITIZED

ORIGINAL - PINS

COPY # 1 - PINS

COPY # 2 - ECAD

CONTAINS NO CBI

ORIGINAL - PINS

COPY # 1 - PINS

COPY # 2 - ECAD (Dave Williams)

CYANAMID

CONTAINS NO CBI

American Cyanamid Company
One Cyanamid Plaza
Wayne, NJ 07470

92 JUN -2 PM 2:25

H. Michael D. Utidjian, M.D.
Corporate Medical Director

8EHQ-0692-4646 Init

May 29, 1992

88920003288

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Document Processing Center (TS-790)
Office of Toxic Substances
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Att'n: Section 8(e) Coordinator (CAP Agreement)

RE: Study or Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

Identification Number: 8ECAP-0041

Dear Sir/Madam:

American Cyanamid Company is submitting the attached study to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program (CAP Agreement) executed by American Cyanamid and EPA. This study does not involve effects observed in humans. These documents do not contain confidential business information.

The enclosed study provides information on a chemical mixture containing ~47% isobutanol [CAS 78-83-1], 4[illegible]% ethanol, 2-(dimethylamino)-,4-methylbenzenesulfonate (salt) [CAS 63150-14-1] and 8% dimethylaminoethanol [CAS 108-01-0]. This material is also known as CT-470-91.

The title of the enclosed report is "Primary Dermal/Ocular Irritation in Albino Rabbits," April 24, 1991.

Under the conditions of the study, this material produced severe and persistent eye irritation.

In total, American Cyanamid is submitting three (3) copies of the enclosed report and this cover letter: an original and two (2) copies.

Further questions regarding this submission may be directed to Ms. Patricia A. Vernon, Associate Toxicologist at the address above or 201-831-2534.

Sincerely,

H. Michael D. Utidjian, M.D.
Corporate Medical Director

PROJECT NUMBER : MB 91-421 D

TEST ARTICLE : CT-470-91

SPONSOR : AMERICAN CYANAMID COMPANY

TITLE : PRIMARY DERMAL/OCULAR IRRITATION IN ALBINO RABBITS

PROTOCOL # : 201-01

ABSTRACT

Method Synopsis -

DERMAL IRRITATION:

Three healthy New Zealand Albino rabbits were dosed dermally with CT-470-91. 0.5 ml of the test article was applied to 1 intact and 1 abraded site on the clipped back of each animal for a total dermal exposure dose of 1.0 ml/rabbit. The sites were occluded for 4 hours. Skin reactions, including ulceration and necrosis, were evaluated using the Draize technique at 1, 24, 48 and 72 hours after patch removal. A modified Primary Irritation Index was calculated using the 24 and 72 hour scores.

OCULAR IRRITATION:

The same three healthy New Zealand Albino rabbits used in the dermal phase were also used for the ocular phase of this study. Initially, the right eye of one rabbit was dosed. Since no evidence of discomfort was observed during dosing, the left eye was dosed, and both eyes of the remaining two rabbits were dosed. 0.1 ml of the test article was placed into the conjunctival sac of each eye. Twenty to thirty seconds after instillation of the test article, the left eye of each rabbit was flushed for one minute with lukewarm water. The right eye remained unwashed. The eyes were examined and scored by the Draize technique at 1 hour post dose and again at 24, 48 and 72 hours post dose. In order to determine reversibility, the eyes were scored again on day 7. The primary eye irritation score for each rabbit, each day, was calculated.

Body weights were recorded pretest. Observations for mortality, toxicity and pharmacological effects were recorded once daily.

Summary -

TOXICITY : One animal died on day 5 with no abnormal predeath physical signs. One instance of diarrhea was the only abnormal systemic sign noted in the two survivors. Based on the lack of clinical signs, the latent mortality and the stress from the severely irritating ocular reactions, it appears that the death is not related to any systemic toxicity of the test article.

DERMAL IRRITATION: Erythema, absent to slight at 1 hour after patch removal, was absent at 24, 48 and 72 hours. There was no edema noted at any observation period. The Modified Primary Irritation Index is 0.

OCULAR IRRITATION: UNWASHED : Corneal opacity, iritis and moderate to severe conjunctival irritation persisted through day 7.

WASHED Corneal opacity, iritis and moderate to severe conjunctival irritation persisted through day 7.

QUALITY ASSURANCE EVALUATION

The Quality Assurance Unit (QAU) has reviewed this report and determined that it accurately describes the methods and standard operating procedures used, and that the results contained herein accurately and fully reflect the raw data from this study.

All procedures performed during the conduct of this study were in conformance with the protocol. Applicable Standard Operating Procedures and GLP regulations were followed. There were no discrepancies between the protocol, the raw data, and/or the final report.

The QAU inspected an in-life phase of the study, audited the raw data and reviewed the report on the dates indicated below. QAU findings were reported to management and the Study Director.

Study Inspected : 3/20/91
Raw Data Audited : 4/11/91

Final report reviewed:

Oscar M. Moreno, Ph.D. 4/23/91

Daniel R. Cerven, M.S., Study Director 24 Apr 91

Bonnie W. Cerven, Quality Assurance 4/23/91

Elizabeth J. Salyer, Archivist 4/24/91

TITLE OF REPORT : PRIMARY DERMAL/OCULAR IRRITATION IN ALBINO RABBITS

PROTOCOL NUMBER: 201-01

OBJECTIVE : To determine the irritancy potential of a test article when applied to the skin and instilled into the eye of the rabbit.

TEST ARTICLE

Source : AMERICAN CYANAMID COMPANY
Date Received : 3/13/91

Test Article Label : CT-470-91

Storage : The test article was stored at ambient room temperature & humidity.

Test Article Description : Clear Liquid

Sample Preparation : Used as received

TEST ANIMALS

Three healthy New Zealand Albino rabbits were selected for this test from a larger group which had been quarantined at least three days. The animals were received from Ace Animals on 3/12/91.

The pretest body weight range was 2.0 - 2.2 kg. The animals were identified by cage notation and a uniquely numbered metal eartag. The animals were housed 1/cage in suspended cages. Bedding was placed beneath the cages and changed twice/week. Fresh Purina Rabbit Chow (Diet #5321) and water were available.

The animal room, reserved exclusively for rabbits on acute tests, was temperature controlled, had a 12 hour light/dark cycle, and was kept clean and vermin free.

TEST DATES

Study Initiation	(Date Protocol Signed)	:	3/13/91
Experimental Start	(1st Exposure to Test Substance)	:	3/19/91
Experimental Term	(Last date data collected)	:	3/26/91
Draft Report Submitted	(If applicable)	:	4/18/91
Study Completion	(Submission of Final Report)	:	4/24/91

SITE PREPARATION

DERMAL IRRITATION: Prior to application of the test article, the back and sides of each animal were clipped free of hair. The left side of each animal was abraded with a bent-tip needle. Three abrasions, approximately 2 - 3 cm apart, extending the length of the exposure site were made. The abrasions were sufficiently deep to penetrate the stratum corneum but not deep enough to produce bleeding. The right side of each animal remained intact.

OCULAR IRRITATION: Immediately prior to instillation of the test article, the eyes of each test animal were examined. Animals with corneal injury or ocular irritation or defects were eliminated from the study.

EXPERIMENTAL DESIGN

DERMAL IRRITATION: The test article was used as received and dosed by volume, 0.5 ml/site, for a total dose of 1.0 ml/rabbit. The test article was applied to one abraded and one intact site on the clipped back of each of three rabbits. The treated sites were covered with two 2.5 cm square gauze patches which were secured with adhesive tape. The torso was wrapped with plastic and secured with adhesive tape. The sites were occluded for 4 hours at which time the wrappings were removed. The residual test article was wiped off prior to dermal observations.

OCULAR IRRITATION: Initially, the right eye of one rabbit was dosed. Since no discomfort was noted at the time of dosing, the left eye was dosed and both eyes of the remaining two rabbits were dosed. The test article was placed by syringe or syringe-type applicator into the conjunctival sac which was formed by gently pulling the lower eyelid away from the eye. After instillation, the lids were held together briefly to insure adequate distribution of the test article. Twenty to thirty seconds after instillation of the test article, the left eye of each rabbit was flushed for one minute with lukewarm water. The right eye of each animal remained unwashed.

TYPE AND FREQUENCY OF OBSERVATIONS

DERMAL IRRITATION: Animals were observed for skin reactions, including ulceration and necrosis, at 1, 24, 48 and 72 hours after patch removal. Erythema and edema were scored according to the numerical Draize technique. Additional signs were described.

OCULAR IRRITATION: Both eyes of each rabbit were examined for irritation of the cornea, iris and conjunctiva at 1 hour post dose, and again at 24, 48 and 72 hours post dose. In order to determine reversibility, the eyes were scored again on day 7. Ocular reactions were graded according to the numerical Draize technique. Additional signs were described.

Body weights were recorded pretest. The general health of the animals was monitored at each observation period.

ANALYSIS OF DATA

DERMAL IRRITATION: The mean scores for erythema and edema for each observation period were calculated. A modified Primary Irritation Index was calculated using the 24 and 72 hours scores.

OCULAR IRRITATION: The primary eye irritation score for each rabbit was calculated from the weighted Draize scale. The method of calculation is indicated on the attached scale.

RETENTION OF DATA

The raw data is filed at MB Research by project number. The final report is filed at MB Research by sponsor name and MB project number.

The test article will be retained for six months from date of this report.

GOOD LABORATORY PRACTICES

This study was conducted in accordance withe the general provisions of the Good Laboratory Practices Regulations of the FDA - 21 CFR Part 58, EPA - 40 CFR Parts 160 and 792, and OECD Publication of Good Laboratory Practices in the Testing of Chemicals, 1982.

REVISION OF THE PROTOCOL

There were no revisions to the protocol.

D E R M A L O B S E R V A T I O N S

INDIVIDUAL SCORES

	RABBIT EARTAG NUMBERS/SEX D0684/M	D0685/M	D0663/F	MEAN SCORES
PRETEST BODY WEIGHT - kg:	2.2	2.0	2.0	
ERYTHEMA & ESCHAR FORMATION				
Intact skin - 1 hr.	0	1	0	
24 hrs.	0	0	0	.00
48 hrs.	0	0	0	
72 hrs.	0	0	0*	.00
Abraded skin - 1 hr.	1	1	0	
24 hrs.	0	0	0	.00
48 hrs.	0	0	0	
72 hrs.	0	0	0	.00
Edema				
Intact skin - 1 hr.	0	0	0	
24 hrs.	0	0	0	.00
48 hrs.	0	0	0	
72 hrs.	0	0	0	.00
Abraded skin - 1 hr.	0	0	0	
24 hrs.	0	0	0	.00
48 hrs.	0	0	0	
72 hrs.	0	0	0	.00
			SUM OF MEAN	.00
			PRIMARY DERMAL IRRITATION INDEX=SUM OF MEAN	.00

* = animal reclipped

An.#/Sex:	ITEM	TISSUE	READING	HOUR 1	D A Y S 1	2	3	7
D0684-M	A	Cornea	Opacity	3	2	2	2	3
	B		Area	2	2	2	2	1
		1. Total=(AxB)x5		30	20	20	20	15
UNWASHED								
RIGHT EYE	C	Iris		1	1	1	1	1
		2. Total = Cx5		5	5	5	5	5
	D	Conjunctiva	Redness	3ab	3b	3b	3ab	3
	E		Chemosis	2	4	4	4	2
	F		Discharge	2	2	2c	2	1
		3. Total=(D+E+F)x2		14	18	18	18	12
		Totals = 1+2+3		49	43	43	43	32
		SYSTEMIC OBSERVATIONS:		A	A	A	A	A
D0684-M	A	Cornea	Opacity	3	2	2	2	2
	B		Area	2	1	1	1	1
		1. Total=(AxB)x5		30	10	10	10	10
WASHED	C	Iris		1	1	1	1	0
LEFT EYE		2. Total = Cx5		5	5	5	5	0
	D	Conjunctiva	Redness	3	3ab	3ab	3ab	2
	E		Chemosis	2	4	3	3	2
	F		Discharge	2	2	2c	2	1
		3. Total=(D+E+F)x2		14	18	16	16	10
		Totals = 1+2+3		49	33	31	31	20

a = brown areas
b = pale areas
c = white discharge
p = panus
A = normal

MB RESEARCH LABS

PROT/PAGE : 201-01/8 of 11
PROJECT : MB 91-421 D

An.#/Sex:	ITEM	TISSUE	READING	HOUR 1	D A Y S 1	2	3	7
D0685-M	A	Cornea	Opacity	3	3	2	2	2
	B		Area	2	1	2	1	1
		1. Total=(AxB)x5		30	15	20	10	10
UNWASHED								
RIGHT EYE	C	Iris		1	1	1	1	1
		2. Total = Cx5		5	5	5	5	5
	D	Conjunctiva	Redness	3ab	3	3b	2b	1
	E		Chemosis	2	4	4	4	2
	F		Discharge	2	2	2c	2	1
		3. Total=(D+E+F)x2		14	18	18	16	8
		Totals = 1+2+3		49	38	43	31	23
		SYSTEMIC OBSERVATIONS:		D	A	A	A	A
D0685-M	A	Cornea	Opacity	3	3	3	4	2
	B		Area	1	1	1	1	1
		1. Total=(AxB)x5		15	15	15	20	10
WASHED	C	Iris		1	1	1	1	0
LEFT EYE		2. Total = Cx5		5	5	5	5	0
	D	Conjunctiva	Redness	3ab	3b	3b	3b	2
	E		Chemosis	2	4	4	4	2
	F		Discharge	2	2	2c	2	1
		3. Total =(D+E+F)x2		14	18	18	18	10
		Totals = 1+2+3		34	38	38	43	20

a = brown areas
b = pale areas
c = white discharge
p = panus
A = normal
D = diarrhea

MB RESEARCH LABS

PROT/PAGE : 201-01/9 of 11
PROJECT : MB 91-421 D

An.#/Sex:	ITEM	TISSUE	READING	HOUR 1	D A Y S 1	2	3	7
D0663-F	A	Cornea	Opacity	3	3	3	0h	DEAD
	B		Area	?	1	1	0	DAY 5
		1. Total=(AxB)x5			15	15	0	
UNWASHED								
RIGHT EYE	C	Iris		1	0	1	0	
		2. Total = Cx5		5	0	5	0	
	D	Conjunctiva	Redness	2ab	2	3	3b	
	E		Chemosis	4	3	4	3	
	F		Discharge	2	2	2c	2	
		3. Total=(D+E+F)x2		16	14	18	16	
		Totals = 1+2+3		21+	29	38	16	
		SYSTEMIC OBSERVATIONS:		A	A	A	A	
D0663-F	A	Cornea	Opacity	3	3	3	3	
	B		Area	2	2	2	1	
		1. Total=(AxB)x5		30	30	30	15	
WASHED	C	Iris		1	0	1	1	
LEFT EYE		2. Total = Cx5		5	0	5	5	
	D	Conjunctiva	Redness	2ab	2	2ab	3ab	
	E		Chemosis	4	3	4	3	
	F		Discharge	2	2	2c	2c	
		3. Total=(D+E+F)x2		16	14	16	16	
		Totals = 1+2+3		51	44	51	36	

a = brown areas
b = pale areas
c = white discharge
h = lack of normal luster
A = normal
? = unable to determine due to severe chemosis
+ = actual total may be higher if all scores were readable

DRAIZE DERMAL SCORING CODE

Evaluation of Skin Reactions:

Erythema & Eschar Formation:

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Edema Formation:

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 millimeter)	3
Severe edema (raised more than 1 millimeter and extending beyond the area of exposure)	4

SCALE FOR SCORING OCULAR LESIONS**

(1) CORNEA

(A) OPACITY- DEGREE OF DENSITY (AREA MOST DENSE TAKEN FOR READING)

NO OPACITY	0
SCATTERED OR DIFFUSE AREA, DETAILS OF IRIS CLEARLY VISIBLE	1*
EASILY DISCERNIBLE TRANSLUCENT AREAS, DETAILS OF IRIS SLIGHTLY OBSCURED	2*
OPALESCENT AREAS, NO DETAILS OF IRIS VISIBLE, SIZE OF PUPIL BARELY DISCERNIBLE	3*
OPAQUE, IRIS INVISIBLE	4*

(B) AREA OF CORNEA INVOLVED

ONE QUARTER (OR LESS) BUT NOT ZERO	1
GREATER THAN ONE QUARTER, BUT LESS THAN HALF	2
GREATER THAN HALF, BUT LESS THAN THREE QUARTERS	3
GREATER THAN THREE QUARTERS, UP TO WHOLE AREA	4

SCORE EQUALS A x B x 5 TOTAL MAXIMUM = 80

(2) IRIS

(A) VALUES

NORMAL	0
FOLDS ABOVE NORMAL, CONGESTION, SWELLING, CIRCUMCORNEAL INJECTION (ANY OR ALL OF THESE OR COMBINATION OF ANY THEREOF) IRIS STILL REACTING TO LIGHT (SLUGGISH REACTION IS POSITIVE)	1*
NO REACTION TO LIGHT, HEMORRHAGE, GROSS DESTRUCTION(ANY OR ALL OF THESE)	2*

SCORE EQUALS A x 5 TOTAL MAXIMUM = 10

(3) CONJUNCTIVAE

(A) REDNESS(REFERS TO PALPEBRAL AND BULBAR CONJUNCTIVAE EXCLUDING CORNEA AND IRIS)

VESSELS NORMAL	0
VESSELS DEFINITELY INJECTED ABOVE NORMAL	1
MORE DIFFUSE, DEEPER CRIMSON RED, INDIVIDUAL VESSELS NOT EASILY DISCERNIBLE	2*
DIFFUSE BEEFY RED	3*

(B) CHEMOSIS

NO SWELLING	0
ANY SWELLING ABOVE NORMAL(INCLUDES NICTITATING MEMBRANE)	1
OBVIOUS SWELLING WITH PARTIAL EVERSION OF LIDS	2*
SWELLING WITH LIDS ABOUT HALF CLOSED	3*
SWELLING WITH LIDS ABOUT HALF CLOSED TO COMPLETELY CLOSED	4*

(C) DISCHARGE

NO DISCHARGE	0
ANY AMOUNT DIFFERENT FROM NORMAL(DOES NOT INCLUDE SMALL AMOUNTS OBSERVED IN INNER CANTHUS OF NORMAL ANIMALS)	1
DISCHARGE WITH MOISTENING OF THE LIDS AND HAIRS JUST ADJACENT TO LIDS	2
DISCHARGE WITH MOISTENING OF THE LIDS AND HAIRS, AND CONSIDERABLE AREA AROUND THE EYE	3

SCORE EQUALS (A + B + C) x 2 TOTAL MAXIMUM = 20

THE MAXIMUM TOTAL SCORE IS THE SUM OF ALL SCORES OBTAINED FOR THE CORNEA, IRIS, AND CONJUNCTIVAE. TOTAL MAXIMUM SCORE POSSIBLE = 110

*AN ANIMAL SHALL BE CONSIDERED AS EXHIBITING A POSITIVE REACTION

**DRAIZE, J.H. ET AL. J. PHARM. EXP. THER. 82:377-390.1944

CONCLUSIONS

NON-IRRITANT	0 OR 1 RABBIT(S) WITH POSITIVE SCORES
INDETERMINATE	2 OR 3 RABBITS WITH POSITIVE SCORES
IRRITANT	4 TO 6 RABBITS WITH POSITIVE SCORES

STUDY TITLE: Primary Dermal/Ocular Irritation-Rabbits

13.0 SPONSOR REQUEST:

13.1: The sponsor requests that this protocol be implemented:

☒ As written; or

☐ With modifications as follows: _____

13.2: Test Article:

13.2.1: Label/Identity: The test article is identified as follows: CT-470-91

13.2.2: Vehicle (if applicable): Water

13.2.3: Characterization: Data regarding test article identity, purity, strength, stability, uniformity & safety:

☐ Attached ☒ Filed With Sponsor ☐ Unknown

13.2.4: Estimated Date of Arrival @ MB Research: 3/18/91

13.2.5: Disposition of Test Article @ Study Termination:

☒ Retain @ MBR for 6 months. Proper Disposal method is: Will Supply

☐ Return remaining test article to sponsor.

13.3: Authorization: This protocol is authorized for implementation at MB Research.

BY: Patricia Ann Vernon 3/11/91 FOR: American Cyanamid
(signature) (date) (Company Name)

PATRICIA ANN VERNON — One Cyanamid Plaza
(typed name) (address)

ASSOCIATE TOXICOLOGIST — Wayne — NJ 07470
(title) (city) (state) (zip)

14.0 MB RESEARCH ACKNOWLEDGMENT: Request for implementation of this protocol and receipt of the above identified test article is acknowledged by MB Research.

14.1: Test article received: 3/13/91 Physical Description: Clear Liquid

14.2: MB Project Number: The following MB Research Project number has been assigned to this study: 91-421CD

14.3: Animal Supplier: The Licensed U.S.D.A. animal supplier is: Ace Animals

14.4: Proposed Study Dates:

14.4.1: Experimental Start Date: 19 Mar 91 14.4.2: Experimental Term Date: 22 Mar 91

14.4.3: Study Completion Date (Submission of Final Report): Within 3 weeks following Experimental Term Date.

14.5: Approval: This protocol is approved for implementation at MB Research by the below named MB Study Director.

David Allen 13 Mar 91
BY: (date)

MB Research Laboratories, Inc.
Steinsburg & Mentz Roads
Spinnerstown, PA 18968
(215) 536-4110

CERTIFICATE OF AUTHENTICITY

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Data produced 10 (Month) 9 (Day) 92 (Year) Marcia Lubelian Camera Operator

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